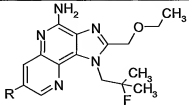







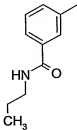


## Examples 343 - 350

|  |                                      |  |                        |
|---|--------------------------------------|--|------------------------|
| Example   | Reagent                              | R  | Measured Mass<br>(M+H) |
|   | None                                 | Br   | 396.0825               |
| 343   | Pyridine-3-boronic acid              |   | 395.1991               |
| 344   | Thiophene-3-boronic acid             |   | 400.1602               |
| 345   | 3-Hydroxyphenylboronic acid          |   | 410.2020               |
| 346   | 4-(Hydroxymethyl)-phenylboronic acid |   | 424.2136               |
| 347   | 4-Methoxyphenylboronic acid          |   | 424.2139               |
| 348   | 3-Chlorophenylboronic acid           |   | 428.1655               |
| 349   | (3-Aminocarbonylphenyl)-boronic acid |  | 437.2093               |

|     |   |   |          |
|-----|---|---|----------|
| 350 | 3-( <i>N</i> -Propylaminocarbonyl)-phenylboronic acid |  | 479.2554 |
|-----|---|---|----------|

## Examples 351 – 365

## Part A

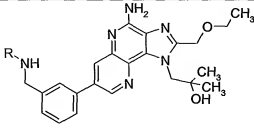







The method described in Examples 339 – 342 was used to treat 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.6 g, 4.06 mmol) with (3-aminomethylphenyl)boronic acid hydrochloride (1.3 g, 6.94 mmol), potassium carbonate (3.0 g, 22 mmol), and dichlorobis(triphenylphosphine)palladium(II) (0.128 g, 0.182 mmol) in DME (20 mL) and water (10 mL). The reaction was heated for 15.5 hours. The eluent used for chromatographic purification was 5% to 25% 1 M methanolic ammonia in dichloromethane. Following chromatographic purification 1.19 g of 1-[4-amino-7-[3-(aminomethyl)phenyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol were obtained as a yellow solid.








## Part B

An acid chloride, sulfonyl chloride, or isocyanate (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-[4-amino-7-[3-(aminomethyl)phenyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (41.7 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.034 mL, 0.20 mmol) in *N,N*-dimethylacetamide (DMA) (1 mL). The test tube was capped and vortexed overnight at room temperature. Water (0.100 mL) was added to each test tube, and the solvent was removed by vacuum centrifugation.

The compounds were purified according to the method described in Examples 77 – 127. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

## Examples 351 - 365

|  |                                   |   |                     |
|---|-----------------------------------|---|---------------------|
| Example   | Reagent                           | R   | Measured Mass (M+H) |
| 351   | None                              | H—  | 421.2331            |
| 352   | Acetyl chloride                   |    | 463.2497            |
| 353   | Cyclopentanecarbonyl chloride     |    | 517.2947            |
| 354   | Benzoyl chloride                  |    | 525.2606            |
| 355   | Cyclohexanecarbonyl chloride      |    | 531.3110            |
| 356   | Nicotinoyl chloride hydrochloride |    | 526.2570            |
| 357   | Ethanesulfonyl chloride           |   | 513.2332            |
| 358   | Isopropylsulfonyl chloride        |  | 527.2480            |

|     |  |   |          |
|-----|--|---|----------|
| 359 | Benzenesulfonyl chloride               |  | 561.2324 |
| 360 | 1-Methylimidazole-4-sulfonyl chloride  |  | 565.2375 |
| 361 | 2,2,2-Trifluoroethanesulfonyl chloride |  | 567.2000 |
| 362 | Methyl isocyanate                      |  | 478.2566 |
| 363 | Cyclopentyl isocyanate                 |  | 532.3046 |
| 364 | Phenyl isocyanate                      |  | 540.2700 |
| 365 | 4-Morpholinylcarbonyl chloride         |  | 534.2824 |

## Examples 366 – 369

## Part A

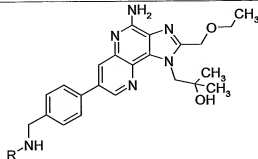



5 A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.6 g, 4.06 mmol), (4-aminomethylphenyl)boronic acid hydrochloride (0.913 g, 4.87 mmol), potassium carbonate (2.5 g, 18 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.028 g, 0.041 mmol), DME (15 mL), and water (7 mL) was stirred under a nitrogen atmosphere and then

heated at 110 °C for 18 hours and allowed to cool to room temperature. An analysis by LC/MS indicated the reaction was incomplete, and additional dichlorobis(triphenylphosphine)palladium(II) (0.050 g) was added. Heating was continued for another six hours, but the reaction did not progress. Additional (4-aminomethylphenyl)boronic acid hydrochloride (0.400 g), potassium carbonate (0.500 g) and dichlorobis(triphenylphosphine)palladium(II) (0.050 g) were added. The reaction was heated at 110 °C for six hours, allowed to cool to room temperature, and concentrated under reduced pressure. Chromatographic purification was carried out as described in Examples 351 - 365 to provide 1.13 g of 1-[4-amino-7-[4-(aminomethyl)phenyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a yellow solid.

#### Part B

The method described in Part B of Examples 351 - 365 was followed using 1-[4-amino-7-[4-(aminomethyl)phenyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol instead of 1-[4-amino-7-[3-(aminomethyl)phenyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

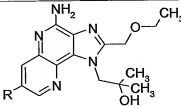




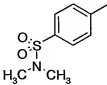
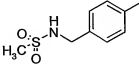
## Examples 366 - 369

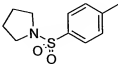
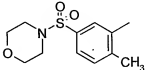
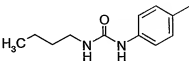
|  |                            |   |                        |
|---|----------------------------|---|------------------------|
| Example   | Reagent                    | R   | Measured Mass<br>(M+H) |
| 366   | None                       | H-  | 421.2330               |
| 367   | Isobutyryl chloride        |  | 491.2799               |
| 368   | Benzoyl chloride           |  | 525.2647               |
| 369   | Isopropylsulfonyl chloride |  | 527.2454               |

## Examples 370 - 378

The methods described in Examples 154 – 194 were followed using 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (39.2 mg, 0.100 mmol) instead of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol with the modification that the samples were not diluted in methanol after the initial heating at 80 °C overnight. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

## Examples 370 - 378

|  |   |   |                     |
|---|---|---|---------------------|
| Example   | Reagent   | R   | Measured Mass (M+H) |
| 370   | (2-Methoxymethylphenyl)-boronic acid              |    | 436.2349            |
| 371   | (2-Acetylamino-phenyl)-boronic acid               |    | 449.2288            |
| 372   | (2-Trifluoromethylphenyl)-boronic acid            |    | 460.1941            |
| 373   | (2-Methylsulfonylphenyl)-boronic acid             |    | 470.1868            |
| 374   | <i>N,N</i> -Dimethyl 4-boronobenzenesulfonamide   |    | 499.2109            |
| 375   | (4-Methanesulfonylamino-methylphenyl)boronic acid |  | 499.2140            |

|     |   |   |          |
|-----|---|---|----------|
| 376 | <i>N</i> -Pyrrolidinyl 4-boronobenzenesulfonamide         |  | 525.2261 |
| 377 | <i>N</i> -Morpholinyl 3-borono-4-methylbenzenesulfonamide |  | 555.2371 |
| 378 | 4-(3-Butylureido)phenyl-boronic acid, pinacol ester       |  | 506.2886 |

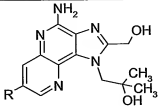




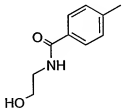
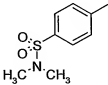
## Examples 379 - 388

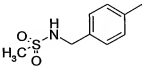
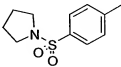
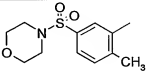
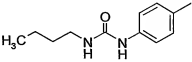
1-[4-Amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (0.039 g, 0.10 mmol) was added to a test tube. The boronic acid (0.11 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added. The test tube was purged with nitrogen. Palladium (II) acetate (0.150 mL of a 4 mg/mL solution in toluene, 0.0026 mmol), 2 M aqueous sodium carbonate solution (0.600 mL), deionized water (113  $\mu$ L), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (53  $\mu$ L, 0.0078 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight.

The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the procedure described in Examples 4 - 58. The resulting basic solutions were concentrated by vacuum centrifugation. Each sample was subjected to the reaction with boron tribromide described in Examples 128 - 151 using 0.400 mL of boron tribromide solution for each test tube. Each reaction was stirred for six hours at room temperature. After methanol and 6 N hydrochloric acid were added to each tube, the contents were vortexed for 30 minutes, and the volatiles were removed by vacuum centrifugation. The compounds were purified by reversed phase prep HPLC according to the method described in Examples 77 - 127. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



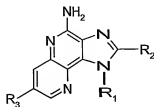
## Examples 379 - 388

|  |  |   |                     |
|---|--|---|---------------------|
| Example   | Reagent  | R   | Measured Mass (M+H) |
| 379   | (2-Methoxymethylphenyl)-boronic acid                 |    | 394.1862            |
| 380   | (2-Acetylaminoethylphenyl)boronic acid               |    | 421.1979            |
| 381   | (2-Trifluoromethylphenyl)-boronic acid               |    | 432.1639            |
| 382   | (3-Methylsulfonylphenyl)-boronic acid                |    | 442.1564            |
| 383   | [4-(2-Methoxyethylaminocarbonyl)-phenyl]boronic acid |   | 451.2094            |
| 384   | N,N-Dimethyl 4-boronobenzenesulfonamide              |  | 471.1804            |

|     |   |   |          |
|-----|---|---|----------|
| 385 | (4-Methanesulfonylamino-methylphenyl)boronic acid         |  | 471.1806 |
| 386 | <i>N</i> -Pyrrolidinyl 4-boronobenzenesulfonamide         |  | 497.1988 |
| 387 | <i>N</i> -Morpholinyl 3-borono-4-methylbenzenesulfonamide |  | 527.2061 |
| 388 | 4-(3-Butylureido)phenylboronic acid, pinacol ester        |  | 478.2562 |

## Exemplary Compounds Table

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (III) wherein  $R_1$ ,  $R_2$ , and  $R_3$  are defined immediately below and in the table. In this table, each row represents one specific compound and a specific embodiment of the invention.



III

wherein:

10  $R_1$  is preferably selected from the following:



2-hydroxy-2-methylpropyl



2-methylpropyl

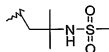


propyl

15

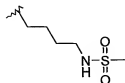


2,3-dihydroxypropyl



2-methanesulfonylamino-2-methylpropyl  
(i.e., 2-methyl-2-[(methylsulfonyl)amino]propyl)

20

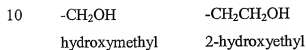
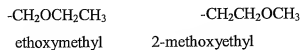
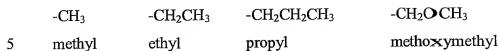


4-methanesulfonylaminobutyl  
(i.e., 4-[(methylsulfonyl)amino]butyl)

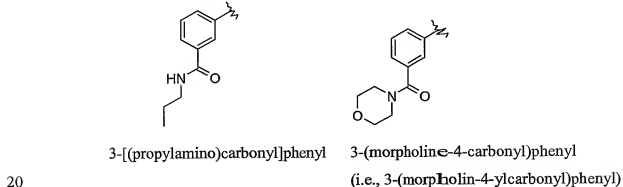
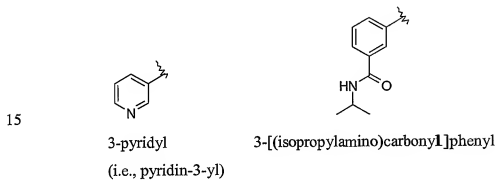


2-fluoro-2-methylpropyl

R<sub>2</sub> is preferably selected from the following:

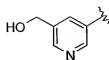


R<sub>3</sub> is preferably selected from the following:

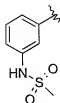




6-fluoropyridin-3-yl



5-(hydroxymethyl)pyridin-3-yl



5 3-[(methylsulfonyl)amino]phenyl

| R <sub>1</sub>           | R <sub>2</sub> | R <sub>3</sub>                     |
|--------------------------|----------------|------------------------------------|
| 2-hydroxy-2-methylpropyl | methyl         | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | methyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | methyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | methyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | methyl         | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | methyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-hydroxy-2-methylpropyl | methyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2-hydroxy-2-methylpropyl | ethyl          | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | ethyl          | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | ethyl          | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | ethyl          | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | ethyl          | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | ethyl          | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-hydroxy-2-methylpropyl | ethyl          | 3-[(methylsulfonyl)amino]phenyl    |
| 2-hydroxy-2-methylpropyl | propyl         | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | propyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | propyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | propyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | propyl         | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | propyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-hydroxy-2-methylpropyl | propyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2-hydroxy-2-methylpropyl | methoxymethyl  | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | methoxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | methoxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | methoxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | methoxymethyl  | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | methoxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |

|                          |                |                                    |
|--------------------------|----------------|------------------------------------|
| 2-hydroxy-2-methylpropyl | methoxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2-hydroxy-2-methylpropyl | ethoxymethyl   | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | ethoxymethyl   | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | ethoxymethyl   | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | ethoxymethyl   | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | ethoxymethyl   | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | ethoxymethyl   | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-hydroxy-2-methylpropyl | ethoxymethyl   | 3-[(methylsulfonyl)amino]phenyl    |
| 2-hydroxy-2-methylpropyl | 2-methoxyethyl | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | 2-methoxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | 2-methoxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | 2-methoxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | 2-methoxyethyl | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | 2-methoxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-hydroxy-2-methylpropyl | 2-methoxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-hydroxy-2-methylpropyl | hydroxymethyl  | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | hydroxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | hydroxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | hydroxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | hydroxymethyl  | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | hydroxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-hydroxy-2-methylpropyl | hydroxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2-hydroxy-2-methylpropyl | 2-hydroxyethyl | pyridin-3-yl                       |
| 2-hydroxy-2-methylpropyl | 2-hydroxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-hydroxy-2-methylpropyl | 2-hydroxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-hydroxy-2-methylpropyl | 2-hydroxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-hydroxy-2-methylpropyl | 2-hydroxyethyl | 6-fluoropyridin-3-yl               |
| 2-hydroxy-2-methylpropyl | 2-hydroxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-hydroxy-2-methylpropyl | 2-hydroxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl           | methyl         | pyridin-3-yl                       |
| 2-methylpropyl           | methyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl           | methyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl           | methyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl           | methyl         | 6-fluoropyridin-3-yl               |
| 2-methylpropyl           | methyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methylpropyl           | methyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl           | ethyl          | pyridin-3-yl                       |
| 2-methylpropyl           | ethyl          | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl           | ethyl          | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl           | ethyl          | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl           | ethyl          | 6-fluoropyridin-3-yl               |
| 2-methylpropyl           | ethyl          | 5-(hydroxymethyl)pyridin-3-yl      |

|                |                |                                    |
|----------------|----------------|------------------------------------|
| 2-methylpropyl | ethyl          | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl | propyl         | pyridin-3-yl                       |
| 2-methylpropyl | propyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl | propyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl | propyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl | propyl         | 6-fluoropyridin-3-yl               |
| 2-methylpropyl | propyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methylpropyl | propyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl | methoxymethyl  | pyridin-3-yl                       |
| 2-methylpropyl | methoxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl | methoxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl | methoxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl | methoxymethyl  | 6-fluoropyridin-3-yl               |
| 2-methylpropyl | methoxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methylpropyl | methoxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl | ethoxymethyl   | pyridin-3-yl                       |
| 2-methylpropyl | ethoxymethyl   | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl | ethoxymethyl   | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl | ethoxymethyl   | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl | ethoxymethyl   | 6-fluoropyridin-3-yl               |
| 2-methylpropyl | ethoxymethyl   | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methylpropyl | ethoxymethyl   | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl | 2-methoxyethyl | pyridin-3-yl                       |
| 2-methylpropyl | 2-methoxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl | 2-methoxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl | 2-methoxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl | 2-methoxyethyl | 6-fluoropyridin-3-yl               |
| 2-methylpropyl | 2-methoxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methylpropyl | 2-methoxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl | hydroxymethyl  | pyridin-3-yl                       |
| 2-methylpropyl | hydroxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl | hydroxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl | hydroxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl | hydroxymethyl  | 6-fluoropyridin-3-yl               |
| 2-methylpropyl | hydroxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methylpropyl | hydroxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methylpropyl | 2-hydroxyethyl | pyridin-3-yl                       |
| 2-methylpropyl | 2-hydroxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methylpropyl | 2-hydroxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-methylpropyl | 2-hydroxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methylpropyl | 2-hydroxyethyl | 6-fluoropyridin-3-yl               |
| 2-methylpropyl | 2-hydroxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |

|                |                |                                    |
|----------------|----------------|------------------------------------|
| 2-methylpropyl | 2-hydroxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| propyl         | methyl         | pyridin-3-yl                       |
| propyl         | methyl         | 3-[(isopropylamino)carbonyl]phenyl |
| propyl         | methyl         | 3-[(propylamino)carbonyl]phenyl    |
| propyl         | methyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl         | methyl         | 6-fluoropyridin-3-yl               |
| propyl         | methyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| propyl         | methyl         | 3-[(methylsulfonyl)amino]phenyl    |
| propyl         | ethyl          | pyridin-3-yl                       |
| propyl         | ethyl          | 3-[(isopropylamino)carbonyl]phenyl |
| propyl         | ethyl          | 3-[(propylamino)carbonyl]phenyl    |
| propyl         | ethyl          | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl         | ethyl          | 6-fluoropyridin-3-yl               |
| propyl         | ethyl          | 5-(hydroxymethyl)pyridin-3-yl      |
| propyl         | ethyl          | 3-[(methylsulfonyl)amino]phenyl    |
| propyl         | propyl         | pyridin-3-yl                       |
| propyl         | propyl         | 3-[(isopropylamino)carbonyl]phenyl |
| propyl         | propyl         | 3-[(propylamino)carbonyl]phenyl    |
| propyl         | propyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl         | propyl         | 6-fluoropyridin-3-yl               |
| propyl         | propyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| propyl         | propyl         | 3-[(methylsulfonyl)amino]phenyl    |
| propyl         | methoxymethyl  | pyridin-3-yl                       |
| propyl         | methoxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| propyl         | methoxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| propyl         | methoxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl         | methoxymethyl  | 6-fluoropyridin-3-yl               |
| propyl         | methoxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| propyl         | methoxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| propyl         | ethoxymethyl   | pyridin-3-yl                       |
| propyl         | ethoxymethyl   | 3-[(isopropylamino)carbonyl]phenyl |
| propyl         | ethoxymethyl   | 3-[(propylamino)carbonyl]phenyl    |
| propyl         | ethoxymethyl   | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl         | ethoxymethyl   | 6-fluoropyridin-3-yl               |
| propyl         | ethoxymethyl   | 5-(hydroxymethyl)pyridin-3-yl      |
| propyl         | ethoxymethyl   | 3-[(methylsulfonyl)amino]phenyl    |
| propyl         | 2-methoxyethyl | pyridin-3-yl                       |
| propyl         | 2-methoxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| propyl         | 2-methoxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| propyl         | 2-methoxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl         | 2-methoxyethyl | 6-fluoropyridin-3-yl               |
| propyl         | 2-methoxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |



|                     |                |                                    |
|---------------------|----------------|------------------------------------|
| propyl              | 2-methoxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| propyl              | hydroxymethyl  | pyridin-3-yl                       |
| propyl              | hydroxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| propyl              | hydroxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| propyl              | hydroxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl              | hydroxymethyl  | 6-fluoropyridin-3-yl               |
| propyl              | hydroxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| propyl              | hydroxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| propyl              | 2-hydroxyethyl | pyridin-3-yl                       |
| propyl              | 2-hydroxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| propyl              | 2-hydroxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| propyl              | 2-hydroxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| propyl              | 2-hydroxyethyl | 6-fluoropyridin-3-yl               |
| propyl              | 2-hydroxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| propyl              | 2-hydroxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl | methyl         | pyridin-3-yl                       |
| 2,3-dihydroxypropyl | methyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl | methyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl | methyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl | methyl         | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl | methyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2,3-dihydroxypropyl | methyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl | ethyl          | pyridin-3-yl                       |
| 2,3-dihydroxypropyl | ethyl          | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl | ethyl          | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl | ethyl          | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl | ethyl          | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl | ethyl          | 5-(hydroxymethyl)pyridin-3-yl      |
| 2,3-dihydroxypropyl | ethyl          | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl | propyl         | pyridin-3-yl                       |
| 2,3-dihydroxypropyl | propyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl | propyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl | propyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl | propyl         | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl | propyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2,3-dihydroxypropyl | propyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl | methoxymethyl  | pyridin-3-yl                       |
| 2,3-dihydroxypropyl | methoxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl | methoxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl | methoxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl | methoxymethyl  | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl | methoxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |

|  |                |                                    |
|--|----------------|------------------------------------|
| 2,3-dihydroxypropyl                      | methoxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl                      | ethoxymethyl   | pyridin-3-yl                       |
| 2,3-dihydroxypropyl                      | ethoxymethyl   | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl                      | ethoxymethyl   | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl                      | ethoxymethyl   | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl                      | ethoxymethyl   | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl                      | ethoxymethyl   | 5-(hydroxymethyl)pyridin-3-yl      |
| 2,3-dihydroxypropyl                      | ethoxymethyl   | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl                      | 2-methoxyethyl | pyridin-3-yl                       |
| 2,3-dihydroxypropyl                      | 2-methoxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl                      | 2-methoxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl                      | 2-methoxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl                      | 2-methoxyethyl | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl                      | 2-methoxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2,3-dihydroxypropyl                      | 2-methoxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl                      | hydroxymethyl  | pyridin-3-yl                       |
| 2,3-dihydroxypropyl                      | hydroxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl                      | hydroxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl                      | hydroxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl                      | hydroxymethyl  | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl                      | hydroxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 2,3-dihydroxypropyl                      | hydroxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2,3-dihydroxypropyl                      | 2-hydroxyethyl | pyridin-3-yl                       |
| 2,3-dihydroxypropyl                      | 2-hydroxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2,3-dihydroxypropyl                      | 2-hydroxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2,3-dihydroxypropyl                      | 2-hydroxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2,3-dihydroxypropyl                      | 2-hydroxyethyl | 6-fluoropyridin-3-yl               |
| 2,3-dihydroxypropyl                      | 2-hydroxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2,3-dihydroxypropyl                      | 2-hydroxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | methyl         | pyridin-3-yl                       |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | methyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | methyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | methyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | methyl         | 6-fluoropyridin-3-yl               |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | methyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | methyl         | 3-[(methylsulfonyl)amino]phenyl    |

|  |               |                                    |
|--|---------------|------------------------------------|
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethyl         | pyridin-3-yl                       |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethyl         | 6-fluoropyridin-3-yl               |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | propyl        | pyridin-3-yl                       |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | propyl        | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | propyl        | 3-[(propylamino)carbonyl]phenyl    |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | propyl        | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | propyl        | 6-fluoropyridin-3-yl               |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | propyl        | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | propyl        | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | methoxymethyl | pyridin-3-yl                       |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | methoxymethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | methoxymethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | methoxymethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | methoxymethyl | 6-fluoropyridin-3-yl               |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | methoxymethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | methoxymethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethoxymethyl  | pyridin-3-yl                       |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethoxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-<br>[(methylsulfonyl)amino]propyl | ethoxymethyl  | 3-[(propylamino)carbonyl]phenyl    |

|  |                |                                    |
|--|----------------|------------------------------------|
| [(methylsulfonyl)amino]propyl            |                |                                    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | ethoxymethyl   | 3-(morpholin-4-ylcarbonyl)phenyl)  |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | ethoxymethyl   | 6-fluoropyridin-3-yl               |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | ethoxymethyl   | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | ethoxymethyl   | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-methoxyethyl | pyridin-3-yl                       |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-methoxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-methoxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-methoxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl)  |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-methoxyethyl | 6-fluoropyridin-3-yl               |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-methoxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-methoxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | hydroxymethyl  | pyridin-3-yl                       |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | hydroxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | hydroxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | hydroxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl)  |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | hydroxymethyl  | 6-fluoropyridin-3-yl               |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | hydroxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | hydroxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-hydroxyethyl | pyridin-3-yl                       |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-hydroxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-hydroxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-hydroxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl)  |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-hydroxyethyl | 6-fluoropyridin-3-yl               |

|  |                |                                    |
|--|----------------|------------------------------------|
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-hydroxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-methyl-2-[(methylsulfonyl)amino]propyl | 2-hydroxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | methyl         | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl           | methyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl           | methyl         | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | methyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 4-[(methylsulfonyl)amino]butyl           | methyl         | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl           | methyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl           | methyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | ethyl          | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl           | ethyl          | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl           | ethyl          | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | ethyl          | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 4-[(methylsulfonyl)amino]butyl           | ethyl          | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl           | ethyl          | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl           | ethyl          | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | propyl         | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl           | propyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl           | propyl         | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | propyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 4-[(methylsulfonyl)amino]butyl           | propyl         | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl           | propyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl           | propyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | methoxymethyl  | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl           | methoxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl           | methoxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | methoxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 4-[(methylsulfonyl)amino]butyl           | methoxymethyl  | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl           | methoxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl           | methoxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | ethoxymethyl   | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl           | ethoxymethyl   | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl           | ethoxymethyl   | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | ethoxymethyl   | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 4-[(methylsulfonyl)amino]butyl           | ethoxymethyl   | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl           | ethoxymethyl   | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl           | ethoxymethyl   | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | 2-methoxyethyl | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl           | 2-methoxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl           | 2-methoxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl           | 2-methoxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |

|                                |                |                                    |
|--------------------------------|----------------|------------------------------------|
| 4-[(methylsulfonyl)amino]butyl | 2-methoxyethyl | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl | 2-methoxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl | 2-methoxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl | hydroxymethyl  | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl | hydroxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl | hydroxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl | hydroxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 4-[(methylsulfonyl)amino]butyl | hydroxymethyl  | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl | hydroxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl | hydroxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 4-[(methylsulfonyl)amino]butyl | 2-hydroxyethyl | pyridin-3-yl                       |
| 4-[(methylsulfonyl)amino]butyl | 2-hydroxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 4-[(methylsulfonyl)amino]butyl | 2-hydroxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 4-[(methylsulfonyl)amino]butyl | 2-hydroxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 4-[(methylsulfonyl)amino]butyl | 2-hydroxyethyl | 6-fluoropyridin-3-yl               |
| 4-[(methylsulfonyl)amino]butyl | 2-hydroxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 4-[(methylsulfonyl)amino]butyl | 2-hydroxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl        | methyl         | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl        | methyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl        | methyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl        | methyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl        | methyl         | 6-fluoropyridin-3-yl               |
| 2-fluoro-2-methylpropyl        | methyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-fluoro-2-methylpropyl        | methyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl        | ethyl          | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl        | ethyl          | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl        | ethyl          | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl        | ethyl          | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl        | ethyl          | 6-fluoropyridin-3-yl               |
| 2-fluoro-2-methylpropyl        | ethyl          | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-fluoro-2-methylpropyl        | ethyl          | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl        | propyl         | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl        | propyl         | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl        | propyl         | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl        | propyl         | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl        | propyl         | 6-fluoropyridin-3-yl               |
| 2-fluoro-2-methylpropyl        | propyl         | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-fluoro-2-methylpropyl        | propyl         | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl        | methoxymethyl  | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl        | methoxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl        | methoxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl        | methoxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl        | methoxymethyl  | 6-fluoropyridin-3-yl               |

|                         |                |                                    |
|-------------------------|----------------|------------------------------------|
| 2-fluoro-2-methylpropyl | methoxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-fluoro-2-methylpropyl | methoxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl | ethoxymethyl   | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl | ethoxymethyl   | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl | ethoxymethyl   | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl | ethoxymethyl   | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl | ethoxymethyl   | 6-fluoropyridin-3-yl               |
| 2-fluoro-2-methylpropyl | ethoxymethyl   | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-fluoro-2-methylpropyl | ethoxymethyl   | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl | 2-methoxyethyl | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl | 2-methoxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl | 2-methoxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl | 2-methoxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl | 2-methoxyethyl | 6-fluoropyridin-3-yl               |
| 2-fluoro-2-methylpropyl | 2-methoxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-fluoro-2-methylpropyl | 2-methoxyethyl | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl | hydroxymethyl  | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl | hydroxymethyl  | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl | hydroxymethyl  | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl | hydroxymethyl  | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl | hydroxymethyl  | 6-fluoropyridin-3-yl               |
| 2-fluoro-2-methylpropyl | hydroxymethyl  | 5-(hydroxymethyl)pyridin-3-yl      |
| 2-fluoro-2-methylpropyl | hydroxymethyl  | 3-[(methylsulfonyl)amino]phenyl    |
| 2-fluoro-2-methylpropyl | 2-hydroxyethyl | pyridin-3-yl                       |
| 2-fluoro-2-methylpropyl | 2-hydroxyethyl | 3-[(isopropylamino)carbonyl]phenyl |
| 2-fluoro-2-methylpropyl | 2-hydroxyethyl | 3-[(propylamino)carbonyl]phenyl    |
| 2-fluoro-2-methylpropyl | 2-hydroxyethyl | 3-(morpholin-4-ylcarbonyl)phenyl   |
| 2-fluoro-2-methylpropyl | 2-hydroxyethyl | 6-fluoropyridin-3-yl               |
| 2-fluoro-2-methylpropyl | 2-hydroxyethyl | 5-(hydroxymethyl)pyridin-3-yl      |

### CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon  $\alpha$  and/or tumor necrosis factor  $\alpha$  in human cells when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon ( $\alpha$ ) and tumor necrosis factor ( $\alpha$ ) (IFN- $\alpha$  and TNF- $\alpha$ , respectively) secreted into culture media as described by Testerman et. al. in

"Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, 58, 365-372 (September, 1995).

#### Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at  $4 \times 10^6$  cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

#### Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014  $\mu$ M. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

#### Incubation

The solution of test compound is added at 60  $\mu$ M to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014  $\mu$ M). The final concentration of PBMC suspension is  $2 \times 10^6$  cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.



## Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN- $\alpha$  by ELISA and for TNF- $\alpha$  by IGEN/BioVeris Assay.

## Interferon ( $\alpha$ ) and Tumor Necrosis Factor ( $\alpha$ ) Analysis

IFN- $\alpha$  concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF- $\alpha$  concentration is determined by ORIGIN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF- $\alpha$  capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

## Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF- $\alpha$  and IFN- $\alpha$  (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- $\alpha$  and 40 pg/mL for TNF- $\alpha$ ) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " \* ", and is noted as not reliably detectable. In subsequent calculations and statistics, " \* ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- $\alpha$ , $\alpha$ -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784;

Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration ( $\mu\text{molar}$ ) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- $\alpha$  and 40 pg/mL for TNF- $\alpha$ ). The maximal response is the maximal amount of cytokine (pg/mL) produced in the dose-response.

## CYTOKINE INDUCTION IN HUMAN CELLS

### (High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

#### Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at  $4 \times 10^6$  cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

#### Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014  $\mu\text{M}$ . Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- $\alpha,\alpha$ -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91)

on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028  $\mu$ M) than the final tested concentration range.

#### Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014  $\mu$ M) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is  $2 \times 10^6$  cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

#### Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

#### Interferon- $\alpha$ and Tumor Necrosis Factor- $\alpha$ Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF- $\alpha$  and human IFN- $\alpha$  that have been pre-coated on specific spots. Each well contains four spots: one human TNF- $\alpha$  capture antibody (MSD) spot, one human IFN- $\alpha$  capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine serum albumin spots. The human TNF- $\alpha$  capture and detection antibody pair is from MesoScale Discovery. The human IFN- $\alpha$  multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN- $\alpha$  subtypes except IFN- $\alpha$  F (IFNA21). Standards consist of recombinant human TNF- $\alpha$  (R&D Systems, Minneapolis, MN) and IFN- $\alpha$  (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN- $\alpha$  detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the

IFN- $\alpha$  concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

#### Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF- $\alpha$  or IFN- $\alpha$  (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- $\alpha$  and 40 pg/mL for TNF- $\alpha$ ) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN- $\alpha$ , TNF- $\alpha$ ) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- $\alpha,\alpha$ -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted

readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- $\alpha$ , $\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration ( $\mu$ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- $\alpha$  and 40 pg/mL for TNF- $\alpha$ ). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

#### TNF- $\alpha$ INHIBITION IN MOUSE CELLS

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) when tested using the method described below.

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) production upon stimulation by lipopolysaccharide (LPS).

##### Single Concentration Assay:

##### Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to  $3 \times 10^5$  cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100  $\mu$ L) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is  $3 \times 10^4$  cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

##### Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5  $\mu$ M. LPS (Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC<sub>70</sub> concentration as measured by a dose response assay.

#### Incubation

A solution of test compound (1  $\mu$ l) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1  $\mu$ L, EC<sub>70</sub> concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

#### TNF- $\alpha$ Analysis

Following the incubation the supernatant is removed with a pipet. TNF- $\alpha$  concentration is determined by ELISA using a mouse TNF-  $\alpha$  kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF- $\alpha$  expression upon LPS stimulation alone is considered a 100% response.

#### Dose Response Assay:

##### Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10<sup>5</sup> cells/mL in RPMI with 10 % FBS. Cell suspension (250  $\mu$ L) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10<sup>5</sup> cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

#### Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10  $\mu$ M. LPS

(Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC<sub>70</sub> concentration as measured by dose response assay.

#### Incubation

A solution of test compound (200 µl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 µL, EC<sub>70</sub> concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

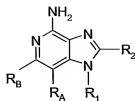
#### TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein:

$R_A$  and  $R_B$  join to form a fused pyridine ring which is substituted by one  $R_3$  group or substituted by one  $R_3$  group and one  $R$  group;

$R_1$  is selected from the group consisting of:

- $R_4$ ,
- $X-R_4$ ,
- $X-Y-R_4$ ,
- $X-Y-X-Y-R_4$ , and
- $X-R_5$ ;

$R_2$  is selected from the group consisting of:

- $R_4$ ,
- $X-R_4$ ,
- $X-Y-R_4$ , and
- $X-R_5$ ;

$R_3$  is selected from the group consisting of:

- $Z-Ar$ ,
- $Z-Ar'-Y-R_4$ ,
- $Z-Ar'-X-Y-R_4$ ,
- $Z-Ar'-R_5$ , and
- $Z-Ar'-X-R_5$ ;

$R$  is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

$Ar$  is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl,

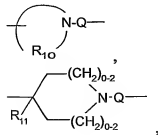
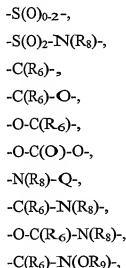


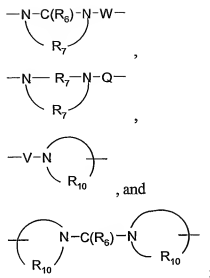
haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, alkoxyalkylenyl,  $\alpha$ -aminocarboxyalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

- 5 Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

- 15 Y is selected from the group consisting of:

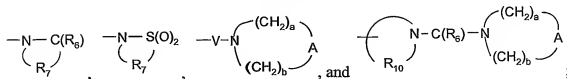




5 Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R<sub>4</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, 10 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, 15 heteroarylalkyleneoxy, heterocyclyl, amino, carboxy, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R<sub>5</sub> is selected from the group consisting of:



20 R<sub>6</sub> is selected from the group consisting of =O and =S;

R<sub>7</sub> is C<sub>2-7</sub> alkylene;

R<sub>8</sub> is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R<sub>9</sub> is selected from the group consisting of hydrogen and alkyl;

$R_{10}$  is  $C_{3-8}$  alkylene;

$R_{11}$  is selected from the group consisting of fluoro, hydroxy, and alkoxy;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and

-N(R<sub>4</sub>)-;

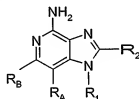
5 Q is selected from the group consisting of a bond, -C(R<sub>6</sub>)-, -C(R<sub>6</sub>)-C(R<sub>6</sub>), -S(O)<sub>2</sub>-,  
-C(R<sub>6</sub>)-N(R<sub>8</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>8</sub>)-, -C(R<sub>6</sub>)-O-, and -C(R<sub>6</sub>)-N(OR<sub>9</sub>)-;

V is selected from the group consisting of -C(R<sub>6</sub>)-, -O-C(R<sub>6</sub>)-, -N(R<sub>8</sub>)-C(R<sub>6</sub>)-, and  
-S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

10 a and b are independently integers from 1 to 6 with the proviso that  $a + b \leq 7$ ;  
or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula I:



I

wherein:

$R_A$  and  $R_B$  join to form a fused pyridine ring which is substituted by one  $R_3$  group  
or substituted by one  $R_3$  group and one R group;

$R_1$  is selected from the group consisting of:

20 -R<sub>4</sub>,  
-X-R<sub>4</sub>,  
-X-Y-R<sub>4</sub>,  
-X-Y-X-Y-R<sub>4</sub>, and  
-X-R<sub>5</sub>;

25  $R_2$  is selected from the group consisting of:

-R<sub>4</sub>,  
-X-R<sub>4</sub>,  
-X-Y-R<sub>4</sub>, and  
-X-R<sub>5</sub>;

R<sub>3</sub> is selected from the group consisting of:

- Z-Ar,
- Z-Ar'-Y-R<sub>4</sub>,
- Z-Ar'-X-Y-R<sub>4</sub>,
- Z-Ar'-R<sub>5</sub>, and
- Z-Ar'-X-R<sub>5</sub>;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclalkylenyl, amino, alkylamino, and dialkylamino;

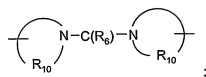
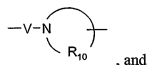
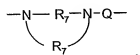
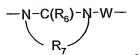
X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

- S(O)<sub>0-2</sub>,
- S(O)<sub>2</sub>-N(R<sub>8</sub>)-,
- C(R<sub>6</sub>)-,
- C(R<sub>6</sub>)-O-,
- O-C(R<sub>6</sub>)-,
- O-C(O)-O-,
- N(R<sub>8</sub>)-Q-,

$$-C(R_6)-N(R_8)-,$$

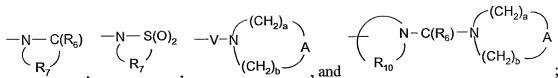
$$-O-C(R_6)-N(R_8)-,$$

$$-C(R_6)-N(OR_9)-,$$


Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R<sub>4</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R<sub>5</sub> is selected from the group consisting of:



R<sub>6</sub> is selected from the group consisting of =O and =S;

R<sub>7</sub> is C<sub>2-7</sub> alkylene;

R<sub>8</sub> is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R<sub>9</sub> is selected from the group consisting of hydrogen and alkyl;

R<sub>10</sub> is C<sub>3-8</sub> alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>4</sub>)-;

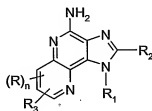
Q is selected from the group consisting of a bond, -C(R<sub>6</sub>)-, -C(R<sub>6</sub>)-C(R<sub>6</sub>), -S(O)<sub>2</sub>-, -C(R<sub>6</sub>)-N(R<sub>8</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>8</sub>)-, -C(R<sub>6</sub>)-O-, and -C(R<sub>6</sub>)-N(OR<sub>9</sub>)-;

V is selected from the group consisting of -C(R<sub>6</sub>)-, -O-C(R<sub>6</sub>)-, -N(R<sub>8</sub>)-C(R<sub>6</sub>)-, and -S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula II:



II

wherein:

n is 0 or 1;

R<sub>1</sub> is selected from the group consisting of:

-R<sub>4</sub>,

-X-R<sub>4</sub>,

-X-Y-R<sub>4</sub>,

-X-Y-X-Y-R<sub>4</sub>, and

-X-R<sub>5</sub>;

R<sub>2</sub> is selected from the group consisting of:

-R<sub>4</sub>,

-X-R<sub>4</sub>,

-X-Y-R<sub>4</sub>, and

-X-R<sub>5</sub>;

R<sub>3</sub> is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R<sub>4</sub>,

-Z-Ar'-X-Y-R<sub>4</sub>,

-Z-Ar'-R<sub>5</sub>, and

-Z-Ar'-X-R<sub>5</sub>;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

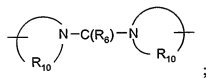
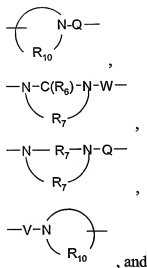
Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-\text{S}(\text{O})_{0.2}-$ ,  
 $-\text{S}(\text{O})_2-\text{N}(\text{R}_8)-$ ,  
 $-\text{C}(\text{R}_6)-$ ,  
 $-\text{C}(\text{R}_6)-\text{O}-$ ,  
 $-\text{O}-\text{C}(\text{R}_6)-$ ,  
 $-\text{O}-\text{C}(\text{O})-\text{O}-$ ,  
 $-\text{N}(\text{R}_8)-\text{Q}-$ ,  
 $-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-$ ,  
 $-\text{O}-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-$ ,  
 $-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-$ ,



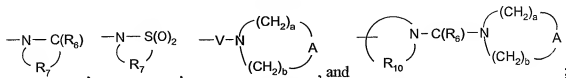
Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

$\text{R}_4$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,



nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

5  $R_5$  is selected from the group consisting of:



$R_6$  is selected from the group consisting of =O and =S;

$R_7$  is  $C_{2-7}$  alkylene;

10  $R_8$  is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

$R_9$  is selected from the group consisting of hydrogen and alkyl;

$R_{10}$  is  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>4</sub>)-;

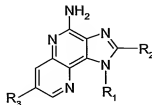
15 Q is selected from the group consisting of a bond, -C(R<sub>6</sub>)-, -C(R<sub>6</sub>)-C(R<sub>6</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>6</sub>)-N(R<sub>8</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>8</sub>)-, -C(R<sub>6</sub>)-O-, and -C(R<sub>6</sub>)-N(OR<sub>9</sub>)-;

V is selected from the group consisting of -C(R<sub>6</sub>)-, -O-C(R<sub>6</sub>)-, -N(R<sub>8</sub>)-C(R<sub>6</sub>)-, and -S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

20 a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

4. A compound of the Formula (III):



III

wherein:

R<sub>1</sub> is selected from the group consisting of:

- R<sub>4</sub>,
- X-R<sub>4</sub>,
- X-Y-R<sub>4</sub>,
- X-Y-X-Y-R<sub>4</sub>, and
- X-R<sub>5</sub>;

R<sub>2</sub> is selected from the group consisting of:

- R<sub>4</sub>,
- X-R<sub>4</sub>,
- X-Y-R<sub>4</sub>, and
- X-R<sub>5</sub>;

R<sub>3</sub> is selected from the group consisting of:

- Z-Ar,
- Z-Ar'-Y-R<sub>4</sub>,
- Z-Ar'-X-Y-R<sub>4</sub>,
- Z-Ar'-R<sub>5</sub>, and
- Z-Ar'-X-R<sub>5</sub>;

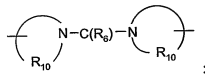
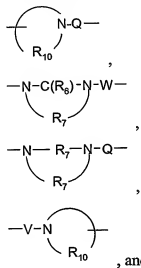
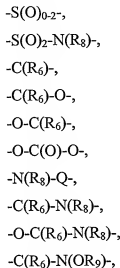
Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:



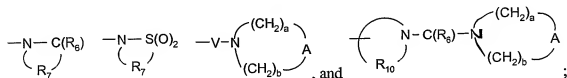
Z is selected from the group consisting of a bond, alkylene, alkenylene, and

alkynylene;

R<sub>4</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$  is selected from the group consisting of:



$R_6$  is selected from the group consisting of =O and =S;

$R_7$  is  $C_{2-7}$  alkylene;

$R_8$  is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

$R_9$  is selected from the group consisting of hydrogen and alkyl;

$R_{10}$  is  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0.2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>4</sub>)-;

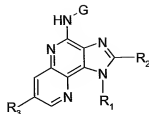
Q is selected from the group consisting of a bond, -C(R<sub>6</sub>)-, -C(R<sub>6</sub>)-C(R<sub>6</sub>), -S(O)<sub>2</sub>-, -C(R<sub>6</sub>)-N(R<sub>8</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>8</sub>)-, -C(R<sub>6</sub>)-O-, and -C(R<sub>6</sub>)-N(OR<sub>9</sub>)-;

V is selected from the group consisting of -C(R<sub>6</sub>)-, -O-C(R<sub>6</sub>)-, -N(R<sub>8</sub>)-C(R<sub>6</sub>)-, and -S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

a and b are independently integers from 1 to 6 with the proviso that  $a + b \leq 7$ ; or a pharmaceutically acceptable salt thereof.

5. A compound of the Formula VII:



VII

wherein:

G is selected from the group consisting of:

- C(O)-R',
- $\alpha$ -aminoacyl,
- $\alpha$ -aminoacyl- $\alpha$ -aminoacyl,
- C(O)-O-R',
- C(O)-N(R'')R',
- C(=NY')-R',
- CH(OH)-C(O)-OY',
- CH(OC<sub>1-4</sub> alkyl)Y<sub>0</sub>,
- CH<sub>2</sub>Y<sub>1</sub>, and
- CH(CH<sub>3</sub>)Y<sub>1</sub>;

R' and R'' are independently selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C<sub>1-6</sub> alkyl, C<sub>1-4</sub> alkoxy, aryl, heteroaryl, arylC<sub>1-4</sub> alkylenyl, heteroarylC<sub>1-4</sub> alkylenyl, haloC<sub>1-4</sub> alkylenyl, haloC<sub>1-4</sub> alkoxy, -O-C(O)-CH<sub>3</sub>, -C(O)-O-CH<sub>3</sub>, -C(O)-NH<sub>2</sub>, -O-CH<sub>2</sub>-C(O)-NH<sub>2</sub>, -NH<sub>2</sub>, and -S(O)<sub>2</sub>-NH<sub>2</sub>, with the proviso that R'' can also be hydrogen;

$\alpha$ -aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C<sub>1-6</sub> alkyl, and benzyl;

Y<sub>0</sub> is selected from the group consisting of C<sub>1-6</sub> alkyl, carboxyC<sub>1-6</sub> alkylenyl, aminoC<sub>1-4</sub> alkylenyl, mono-N-C<sub>1-6</sub> alkylaminoC<sub>1-4</sub> alkylenyl, and di-N,N-C<sub>1-6</sub> alkylaminoC<sub>1-4</sub> alkylenyl;

$Y_1$  is selected from the group consisting of mono-*N*- $C_{1-6}$  alkylamino, di-*N,N*- $C_{1-6}$  alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4- $C_{1-4}$  alkylpiperazin-1-yl;

$R_1$  is selected from the group consisting of:

- 5            - $R_4$ ,  
              - $X-R_4$ ,  
              - $X-Y-R_4$ ,  
              - $X-Y-X-Y-R_4$ , and  
              - $X-R_5$ ;

10            $R_2$  is selected from the group consisting of:

- $R_4$ ,  
              - $X-R_4$ ,  
              - $X-Y-R_4$ , and  
              - $X-R_5$ ;

15            $R_3$  is selected from the group consisting of:

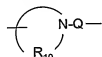
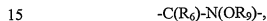
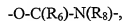
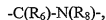
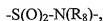
- $Z-Ar$ ,  
              - $Z-Ar'-Y-R_4$ ,  
              - $Z-Ar'-X-Y-R_4$ ,  
              - $Z-Ar'-R_5$ , and  
              - $Z-Ar'-X-R_5$ ;

20            $Ar$  is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,  
 25           aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

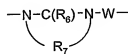
$Ar'$  is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl,  
 30           haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

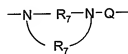
5 Y is selected from the group consisting of:



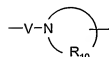
,



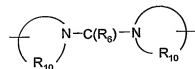
,



,



, and



;

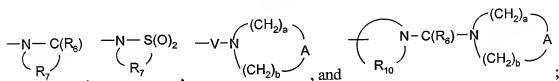
20

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R<sub>4</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$  is selected from the group consisting of:



$R_6$  is selected from the group consisting of =O and =S;

$R_7$  is  $C_{2-7}$  alkylene;

$R_8$  is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

$R_9$  is selected from the group consisting of hydrogen and alkyl;

$R_{10}$  is  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>4</sub>)-;

Q is selected from the group consisting of a bond, -C(R<sub>6</sub>)-, -C(R<sub>6</sub>)-C(R<sub>6</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>6</sub>)-N(R<sub>8</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>8</sub>)-, -C(R<sub>6</sub>)-O-, and -C(R<sub>6</sub>)-N(OR<sub>9</sub>)-;

V is selected from the group consisting of -C(R<sub>6</sub>)-, -O-C(R<sub>6</sub>)-, -N(R<sub>8</sub>)-C(R<sub>6</sub>)-, and -S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

a and b are independently integers from 1 to 6 with the proviso that a + b ≤ 7; or a pharmaceutically acceptable salt thereof.

6. The compound or salt of claim 3 wherein n is 0.

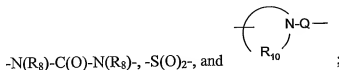
7. The compound or salt of any one of claims 1 through 6 wherein:



$R_1$  is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, fluoroalkyl, heterocyclalkylenyl which is unsubstituted or substituted by hydroxy,  $-X-Y-R_4$ , and  $-X-R_5$ , wherein:

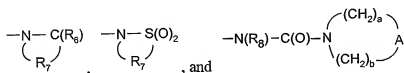
X is alkylene;

Y is selected from the group consisting of  $-N(R_8)-C(O)-$ ,  $-N(R_8)-S(O)_2-$ ,



$R_4$  is selected from the group consisting of alkyl, aryl, and heteroaryl; and

$R_5$  is selected from the group consisting of:



8. The compound or salt of claim 7 wherein  $R_1$  is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl,  $-X-Y-R_4$ , and  $-X-R_5$ .

9. The compound or salt of claim 8 wherein  $R_1$  is selected from the group consisting of alkyl and hydroxyalkyl.

10. The compound or salt of claim 7 wherein  $R_1$  is selected from the group consisting of propyl, 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,3-dihydroxypropyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-[(methylsulfonyl)amino]butyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, (1-hydroxycyclopentyl)methyl, (1-hydroxycyclobutyl)methyl, 2-fluoro-2-methylpropyl, tetrahydro-2H-pyran-4-ylmethyl, and 4-hydroxytetrahydro-2H-pyran-4-ylmethyl.

11. The compound or salt of claim 10 wherein  $R_1$  is selected from the group consisting of propyl, 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,3-dihydroxypropyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-[(methylsulfonyl)amino]butyl, and 2-fluoro-2-methylpropyl.

12. The compound or salt of any one of claims 1 through 11 wherein R<sub>2</sub> is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl.

13. The compound or salt of claim 12 wherein R<sub>2</sub> is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

14. The compound or salt of claim 12 wherein R<sub>2</sub> is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

15. The compound or salt of claim 14 wherein R<sub>2</sub> is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl.

16. The compound or salt of claim 14 wherein R<sub>2</sub> is selected from the group consisting of methyl, ethyl, propyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

17. The compound or salt of any one of claims 1 through 16 wherein Z is selected from the group consisting of a bond, methylene, and ethylene.

18. The compound or salt of claim 17 wherein Z is a bond.

19. The compound or salt of any one of claims 1 through 18 wherein R<sub>3</sub> is -Z-Ar.

20. The compound or salt of any one of claims 1 through 16 wherein R<sub>3</sub> is selected from the group consisting of phenyl, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, thienyl, pyrimidinyl, furyl, and quinolinyl; each of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, alkenyl, hydroxy, hydroxyalkyl, alkoxy, amino, aminoalkyl, cyano, methylenedioxy, arylalkyleneoxy, carboxy, haloalkyl, and dialkylamino.

21. The compound or salt of claim 20 wherein R<sub>3</sub> is selected from the group consisting of phenyl, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, thienyl, pyrimidinyl, and furyl; each of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, alkenyl, hydroxy, hydroxyalkyl, alkoxy, amino, aminoalkyl, and cyano.

22. The compound or salt of any one of claims 1 through 16 wherein R<sub>3</sub> is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, 3-(morpholin-4-ylcarbonyl)phenyl, 3-[(isopropylamino)carbonyl]phenyl, 3-[(propylamino)carbonyl]phenyl, phenyl, 3-(hydroxymethyl)phenyl, 6-fluoropyridin-3-yl, 4-chlorophenyl, 2-hydroxyphenyl, 2-isopropoxyphenyl, 3,4-difluorophenyl, 3-[(methylsulfonyl)amino]phenyl, 4-[(methylsulfonyl)amino]phenyl, and 3-(aminocarbonyl)phenyl.

23. The compound or salt of claim 22 wherein R<sub>3</sub> is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, and 3-(morpholin-4-ylcarbonyl)phenyl.

24. The compound or salt of claim 22 wherein R<sub>3</sub> is selected from the group consisting of pyridin-3-yl, 3-[(isopropylamino)carbonyl]phenyl, 3-[(propylamino)carbonyl]phenyl, 3-(morpholin-4-ylcarbonyl)phenyl, 3-[(methylsulfonyl)amino]phenyl, 5-(hydroxymethyl)pyridin-3-yl, and 6-fluoropyridin-3-yl.

25. The compound or salt of any one of claims 1 through 18 wherein R<sub>3</sub> is -Z-Ar'-Y-R<sub>4</sub>, -Z-Ar'-X-Y-R<sub>4</sub>, -Z-Ar'-R<sub>5</sub>, or -Z-Ar'-X-R<sub>5</sub>.

26. The compound or salt of claim 25 wherein:

Ar' is phenylene or pyridylene;

Y in -Z-Ar'-Y-R<sub>4</sub> or -Z-Ar'-X-Y-R<sub>4</sub> is selected from the group consisting of:

-S(O)<sub>0-2</sub>,

-S(O)<sub>2</sub>-N(R<sub>8</sub>)-,

-C(O)-,

-N(R<sub>8</sub>)-Q-,  
 -C(R<sub>6</sub>)-N(R<sub>8</sub>)-,  
 -C(O)-O-, and  
 -C(O)-N(OCH<sub>3</sub>)-;

wherein:

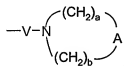
Q is selected from the group consisting of a bond, -C(O)-,  
 -C(O)-O-, -C(O)-N(H)-, and -S(O)<sub>2</sub>-; and

R<sub>8</sub> is selected from the group consisting of hydrogen,  
 C<sub>1-4</sub> alkyl, and alkoxyalkylenyl;

X in -Z-Ar'-X-Y-R<sub>4</sub> or -Z-Ar'-X-R<sub>5</sub> is C<sub>1-4</sub> alkylene;

R<sub>4</sub> in -Z-Ar'-Y-R<sub>4</sub> or -Z-Ar'-X-Y-R<sub>4</sub> is selected from the group consisting of alkyl,  
 haloalkyl, aryl, arylalkylenyl, heteroarylalkylenyl, heteroaryl, alkylheteroarylenyl, and  
 heterocyclyl, with the proviso that R<sub>4</sub> may also be hydrogen when Y is -C(O)-O-,  
 -C(O)-N(OCH<sub>3</sub>)-, or -N(R<sub>8</sub>)-; and

R<sub>5</sub> in -Z-Ar'-R<sub>5</sub> or -Z-Ar'-X-R<sub>5</sub> is



27. The compound or salt of claim 25 wherein R<sub>3</sub> is -Z-Ar'-Y-R<sub>4</sub>, -Z-Ar'-X-Y-R<sub>4</sub>, or  
 -Z-Ar'-R<sub>5</sub>.

28. The compound or salt of claim 27 wherein:

Ar' is phenylene or pyridylene;

Y in -Z-Ar'-Y-R<sub>4</sub> or -Z-Ar'-X-Y-R<sub>4</sub> is selected from the group consisting of:

-S(O)<sub>0.2</sub>-,  
 -C(O)-,  
 -N(R<sub>8</sub>)-Q-, and  
 -C(R<sub>6</sub>)-N(R<sub>8</sub>)-;

wherein:

Q is selected from the group consisting of a bond, -C(O)-,  
 -C(O)-O-, and -S(O)<sub>2</sub>-; and

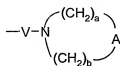
$R_8$  is selected from the group consisting of hydrogen,

$C_{1-4}$  alkyl, and alkoxyalkylenyl;

X in  $-Z-Ar'-X-Y-R_4$  is  $C_{1-4}$  alkylene;

$R_4$  in  $-Z-Ar'-Y-R_4$  or  $-Z-Ar'-X-Y-R_4$  is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroarylalkylenyl, heteroaryl, and heterocyclyl; and

$R_5$  in  $-Z-Ar'-R_5$  is



29. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 28 in combination with a pharmaceutically acceptable carrier.

30. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 28 or a composition of claim 29 to the animal.

31. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 28 or a composition of claim 29 to the animal.

32. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 28 or a composition of claim 29 to the animal.